VIII. Recognized Study Difficulties and Corrective Measures

A. Medical Precedence

(1) Problem

A departure from the ususal methodological approach characterizes this particular epidemiological investigation. Clearly there is no historical "roadmap of methodology" to conduct this study. Most occupational exposure studies use the presentation of an unusual disease to justify the initiation of a comprehensive study. A rare disease or a common disease in an uncommon site, or one with an unusual presentation appearing in space-time clusters, (often in an unusual population or age group) usually generates the requirement for a new study. In the case of Herbicide Orange, the evidence for long-term human effects is tenuous and controversial. Despite the unique problems that this study possesses, such as the lack of clinically defined endpoints, there are many problems that it shares with other occupationally related exposure studies. For example, the question of a latent period in the development of symptoms/signs, the lack of accurate dose-response relationships, and the possibility of a synergistic effect with other toxins/carcinogens are all operating in this study. Since most cohort studies of occupational mortality use the general population as a standard for deriving the expected number of deaths, preemployment selection ("healthy worker" bias) affects the comparative experience. Age-standardized mortality ratios (SMR's) in general are 60-90 percent of the standard in the working population. Similar conflicting results can occur using the matched cohort method proposed in this study design. Statistical verification of the validity of utilizing such a control for a summary mortality index (e.g., SMR) has been infrequently attempted in the past. Inability to verify the validity of the more classical methods of comparing mortality will necessitate the use of multiplicative and/or logistic models to obtain a valid standardized mortality ratio.

(2) Corrective Measures

Study approaches generated by unprecedented occurrences of occupationally related medical complaints require novel approaches, and reorientation beyond standard methods. The success key to this study design is a series of effective, progressive, and helpful peer reviews (all of which have occurred to date and have been incorporated herein). Beyond even the immediacy of the current study, is the growing problem of a myriad of occupationally-related exposures, both in the military and civilian sector, which will require similar epidemiological studies in the future in order to make some judgment as to whether or not an association is of causal significance.

B. Group Accountability Bias

(1) Problem

The numerous media presentations on "Herbicide Orange" issues have focused attention on the RANCH HAND group. Several attempts have been

made to construct lists of former members of this group, and thus, the RANCH HAND population should be somewhat easier to locate and contact than the control population. This difference will be particularly evident with respect to reported mortality experience. The incentives for cooperation and study participation are likely to be greater in the exposed group than in the controls. Also, the close knit reunion association of former RANCH HAND personnel will lead to a more precise reporting of morbidity and mortality in that group. Such group identity tends to decrease the degree of unaccountability in the exposed group while its absence in the controls may lead to under ascertainment of mortality. This could then lead to the attribution of excess mortality in the exposed population.

(2) Corrective Measures

Unaccountability bias will be minimized by keeping the percentages of unaccounted for study subjects below 1% in both exposed and control groups. The morbidity and mortality status of all individuals selected for the study will be strongly pursued utilizing a variety of techniques previously described in this document.

C. "Risk Taking" Behavior Bias

(1) Problem

The early RANCH HAND aircrew population was an exclusively volunteer group; the C-130 control population, while volunteers in the Air Force, were not volunteers for special hazardous missions. RANCH HAND mission conditions were considered to be more dangerous than those encountered in the normal combat environment. This suggests that some differences may exist in the psychological profiles of the two groups. A sensation seeking or risk taking psychological orientation may have altered the accident mortality or morbidity patterns of the exposed group. In addition, an accident rate affected by peripheral neuropathy could be masked by undetected risk taking behavior bias.

(2) Corrective Measures

In an attempt to correct for the unique psychological factors that affect the choice of an aeronautical career, and to adjust for the effects of combat stress, transport aircrew members were matched with crewmembers of similar transport aircraft. However, the volunteer nature of the pre-1965 RANCH HAND operation suggests that this basic matching (as an attempt to control for the psychological effects of combat stress) is not totally ideal. The factors of volunteerism and risk-taking behavior must be considered from both the individual and group perspectives. The assessment of individual risk-taking behavior has been quantified by psychological instruments such as the Sensation Seeking Scale (SSS) of Zuckerman, et al. and the Life Experience Inventory (Torrance). The SSS has been demonstrated to have considerable validity in measuring a variety of phenomena including volunteerism and participation in risky activities and has been applied to naval

aviation trainees (Waters). This study was unable to demonstrate an increased accident-related mortality in this group of individuals.

D. Response Bias

(1) Problem

False positive response is anticipated as the primary bias operating in this study. Compensation issues arising from individual claims to the VA or from class action suits, heightened health concern generated by extensive publicity, disenchantment with military service, and the simple desire to please the interviewer may introduce positive responses that exceed the study's ability to correct or adjust. False negative response will also operate, and such bias is even more difficult to assess than the spurious response in a positive direction. Significant factors in this direction include: issues of patriotism and loyalty, personal conviction as to the propriety of the defoliation program and their participation in it, the strong virility orientation of the pilot/aircrew population (particularly with reference to questions of libido and fertility), personal inconvenience caused by study participation, errors of memory, and fear of the adverse effects on career goals that abnormal physical examination results could produce (a significant problem for active civilian and military pilots).

(2) Pending Retirement Bias

The military retirement system also creates a potential source of bias when personnel who are approaching the end of their careers exaggerate their symptoms so that they may become eligible for disability benefits.

(3) Corrective Measures

The primary correction technique for questionnaire response bias will be a carefully constructed and standardized physical examination. Multiple verification and bias indicator questions will be designed and included in the initial questionnaire. Memory verification will be conducted by cross-referencing responses to medical and personnel records. Detailed statistical correlations between the questionnaire responses and the physical examination results will be conducted. All interviews and physical examinations will be conducted on a "blind" basis to the maximum extent possible. Self-administered and group-administered questionnaires, which would allow for uncontrolled response changes, will not be conducted. The payment of a $100 per day stipend to all eligible participants will be arranged to increase participation rates. Medical data will not be released to agencies such as the Federal Aviation Administration, and therefore civilian flying activities will not be adversely affected by participation in this study. Models of anticipated biases and their estimated impact on the study will be attempted prior to the final analysis of any phase in order to justify the analytic methods used. Conclusions drawn from this study will be predicted and coupled to a bias estimate.

E. Interviewer Bias

(1) Problem

Voice inflection, speed of interview, intonation and ethnicity are recognized factors which can affect positive or negative interview response. These factors will definitely operate in this study.

(2) Corrective Measures

The questionnaire itself will be developed and refined by a civilian contractor. This contractor will assure that the instrument will elicit sensitive personal and medical information in an accurate and efficient manner, while minimizing discomfort to both the subject and the interviewer. All questionnaires will be administered by well-trained and experienced personnel employed by an opinion research organization under contract to conduct this aspect of the study.

F. Changes to the Protocol

(1) Problem

The question of adverse health effects due to Herbicide Orange exposure in Vietnam has evoked many strong emotions. The actions of consumer groups, environmentalists, and other special interest groups have generated defensive responses on the part of some governmental agencies, and reactive decisions by others. Frequently, these responses have been based on unsubstantiated claims and/or scientific evidence of questionable validity. As a result of these governmental actions, the impact on the planning of this study has been substantial. Suggestions to increase the scope of the effort to include other "exposed" individuals or poorly defined ancillary groups continue to surface. However, problems of group ascertainment, exposure validation, control group selection, and control of additional bias make the inclusion of such individuals undesirable from a sound scientific perspective. If such decisions are made without regard for their scientific impact, compromise of study validity is assured.

(2) Corrective Measures

The scientific groups participating in the extensive peer review process agreed with these concerns. The formation of an effective scientific monitoring group will insure that scientific issues will take precedence over emotional pressures to alter the study design when such changes will limit the scientific validity of the study. The dilution of the scientific credibility of this effort by unscientific decisions will be diplomatically resisted. While all suggested improvements will be considered, any alterations or corrections to the study protocol will be based on sound scientific assessments of the proposed changes. Alterations of the protocol will be made only after careful review and analysis by the principal investigators and the monitoring group.

G. Loss to Study/Statistical and Bias Considerations

(1) Problem

Losses to study in the RANCH HAND group pose a major problem to the validity of the inferences that can be made from any subsequent comparisons between or within groups. The avenues of loss will conceivably arise from individual apathy (volunteer bias), lack of appropriate financial reimbursement for loss of salary, the presence or absence of illness (perception of health), and the lack of a desire for "treatment". Losses of matched controls during the questionnaire and physical examination phases of the study, though predictably greater than in the exposed group, may be managed by replacement from the predetermined set of controls. The estimated participation of individuals is shown in Section XV, Figure A-2. It is estimated that the overall response rate of the exposed group will be 65% in the initial questionnaire and 40% in the physical examination phase of the study. These high non-compliance estimates are expected to occur despite great efforts to keep the questionnaire at an acceptable length, and to coordinate questionnaire administration and physical examination with the subject's personal schedule. Losses to study in either the exposed or control groups will obviously lead to decrements in statistical power, and will raise the possibility of severe bias. Losses from the control group are expected to be greater than losses from the exposed set. Such losses would skew the distribution of controls, (Figure 5) and thus alter the characteristics of the population available for study. If differential losses in the control group occur (i.e., "well" controls dropout more frequently than "ill" controls), a "true" herbicide effect would be diluted (Figure 15). Conversely, if "ill" controls are differentially lost, a spurious effect would be attributed to herbicide exposure. To a lesser extent, losses in the exposed group could create similar effects; however, loss to study in the RANCH HAND population should be much less of a problem then in controls, due to their vested interest.

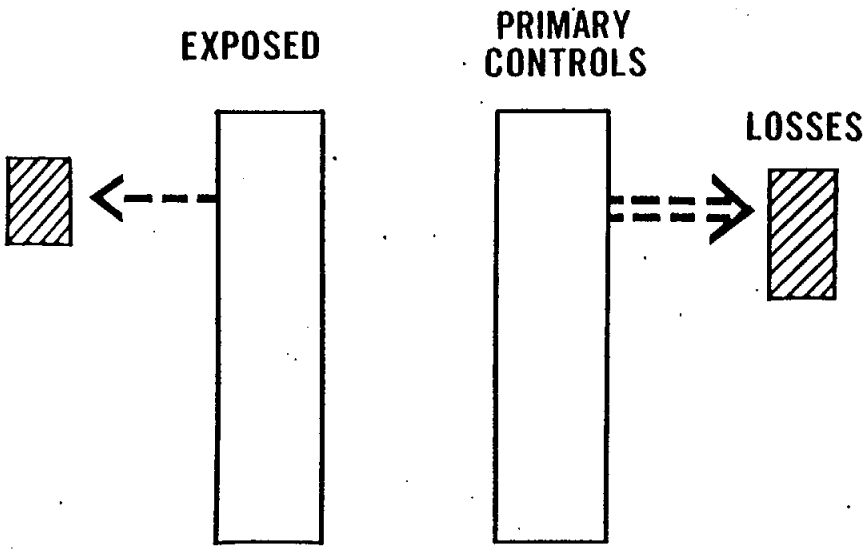
(2) Corrective Measures

The USAF is committed to expending maximal effort to encourage participation. Loss to study problems in the study participants will be avoided as much as possible by detailed and exhaustive efforts to contact and followup each identified participant. NON-PARTICIPANTS WILL BE STRONGLY ENCOURAGED TO RECONSIDER THEIR INITIAL DECISIONS. Design considerations have been made to minimize loss to study in both the exposed and control populations. Although the USAF can not fully compensate study subjects for lost wages during the physical examination, transportation costs, per diem, and lodging costs will be reimbursed, and a $100 per day stipend will be paid to all eligible participants. The replacement concept will help to counteract the decrement in statistical power, and offset the bias created by differential patterns of loss. The exposed group is already of maximum size and cannot be increased, but non-compliant controls can be replaced. This will maximize the degree of pairing between the two study groups. If a non-compliant control is replaced by a control with a similar perception of

FIGURE 15

RATIONALE OF REPLACEMENT

DILUTIONAL BIAS



CONDITIONAL PROBABILITIES:

L = LOSS
W = WELL
I = ILL

his own state of health, the alteration of the control group distribution is offset; (i.e., an "ill" control is replaced with an "ill" individual, and a "well" control with another "well" individual.) This concept of replacement, coupled with the payment of stipends, and extensive efforts to encourage compliance will minimize losses to study and offset the adverse effects of those losses that do occur.

H. Statistical Power Limitations

(1) Problem

As discussed in Section VI, statistical power considerations are heavily dependent on loss to study rates. Since the design of the study is also limited by the size of the exposed population, statistical power for identifying the relative risk of an uncommon disease or symptom-complex (<1/100) is very low (<.50), (See Section VI. B.). This study will, to a greater extent, be able to detect increased risks in common diseases or symptom-complexes (>1/100).

(2) Discussion

The "herald sign" of TCDD exposure, chloracne, is expected to have the greatest likelihood of achieving adequate statistical power in this study. Recent findings from Seveso, Italy, support the importance of chloracne as the primary marker symptom. The incidence of chloracne has been reported by Reggiani (personal communication) and Homberger, et al., to be 14.9 cases per 1000 residents in the region of highest contamination of Seveso (Zone A) and 6 to 12 cases per 1000 in the Seveso community as a whole. These rates vary by age group, with children being at highest risk. Only 1 to 5 cases per 1000 were seen in other regions of Northern Italy (Milan, Como, and Lecco). The incidence of adolescent acne in all of these populations varies between 21% and 30%. These incidence rates probably place chloracne at the lower limit of adequate statistical power of this study. In the Nitro, West Virginia studies, residuals of chloracne, as well as exacerbations of previously active disease, continue to be seen 10 years after the most recent exposures, and 30 years after the industrial accident. Thus, it is likely that any chloracne in the exposed population may be detected, despite the intervening years since RANCH HAND exposures. In addition to chloracne, other recently reported human effects of TCDD exposure at Seveso, Italy, appear to fall within the capabilities of this study design (e.g., peripheral neuropathy, neuropsychiatric effects, and liver dysfunction). In general, with respect to statistical power, continuous data (clinical or laboratory measurements) even from relatively small samples fair much better than either categorical or dichotomous data (presence or absence of a given condition). Consequently, a concerted effort will be made to obtain physical examination data in a scored and/or continuous manner.

I. Variability of Procedures

(1) Problem

The variation of physical examination findings from differences in technique and the random errors inherent in laboratory testing are items of concern, particularly if attributable health effects are subtle or of low magnitude. Nonstandardized procedures and techniques are major contributors to this variance.

(2) Corrective Measures

Variability in examination procedures will be minimized by the use of standardized procedures, examination protocols, on-site monitors, and training. All laboratory procedures will be conducted at the examination center and quality control will be stressed at all times. (See Section IX)

J. Confounding Exposure Factors

(1) Problem

While virtually all of the media attention has been directed toward the 2,4,5-T-containing herbicide formulations, other herbicides were applied concurrently by the C-123 aircrews in Vietnam. Herbicide Blue (Cacodylic acid with 15.4% pentavalent arsenic) and Herbicide White (2,4-D and Picloram) were used throughout the 1962-1970 time period. Any long-term health effects from these additional compounds may confound the results of the study. Peripheral neuritis, tremors, skin and lung cancer, loss of hair and nails, skin rashes, and gastric symptoms have been alleged after exposure to arsenical pesticides. The organophosphate insecticide Malathion was also sprayed by some of these same aircrewmembers when RANCH HAND duties permitted their temporary assignment to mosquito/malaria control missions. Many of these individuals were involved in the aerial spray application of these and other pesticides both before, during, and after their Vietnam service. Long-term effects from these chemicals would confound the study results. The small size of the RANCH HAND population will allow very little opportunity for analytic stratification for these confounding variables. Differing patterns of exposure to aircraft fuels in the study populations have been suggested as confounding factors. The C-130 aircraft were powered by turbo-prop engines which used jet fuel (JP-4), while the C-123 and C-7 aircraft were powered by standard reciprocating engines which used leaded aviation fuel (AV-GAS). After June 1968, many C-123s were modified by the addition of auxilliary jet engine boosters for added power on takeoffs and in emergencies.

(2) Discussion and Corrective Measures

While the extent of confounding caused by exposure to these other pesticides is undetermined at this time, assessment of its magnitude must rely on responses of the subjects to that portion of the questionnaire dealing with other occupational exposures. For this reason, information

concerning exposures to other herbicides/insecticides used in Vietnam will be collected. Whenever possible, stratification techniques will be used to adjust for these confounding variables during data analysis. Variations in fuel between C-130 and C-123 aircraft would be significant factors if individuals in the study were heavily and repetitively exposed. However, the normal duties of the study participants did not involve aircraft refueling or other fuel handling activities. Thus, fuel exposures can be minimized as significant confounding factors.